REMARKS

Applicants have amended claims 28, 29, 42, 49 and 50. Upon entry of this amendment, claims 28-30, 42, 43, 49 and 50 remain pending. Applicants request entry of the amendment after final rejection, filed March 28, 2002, prior to or concurrent with this amendment. Applicants appreciate the withdrawal of the anticipation rejection. The office action is discussed below.

The claims are readily understood by the skilled person, and thus are definite

Applicants reiterate that in order to be definite a claim need only reasonably apprise those skilled in the art of the utilization and scope of the invention. *Hybritech, Inc. v. Monoclonal Antibodies,* 231 USPQ 81, 94-95 (1986). Words are to be given their plain meaning as understood by the person of ordinary skill in the art, particularly given the limitations of the English language. *See* MPEP §§ 707.07(g); 2111.01 (August 2001). Claims are to be given their broadest reasonable interpretation consistent with the specification. *See* MPEP § 2111 (August 2001). In sum, in order to reject the claims on definiteness grounds, it is incumbent on the Examiner to show how and why the skilled person having applicants' specification would not be apprised of the invention by the language-at-issue. The rejections are discussed below in the order presented by the examiner.

(a) The examiner considered the recitation of SCR and SEQ ID NO: 59 to be indefinite. The claims have been amended to indicate the SEQ ID NO: 59

is the LHR-A of CR1, as explained on page 4, line 18 of the Specification and the Sequence Listing amendment submitted June 12, 2000. The sequence of LHR-A of CR1 is contained on pages 4-5 of the application, which sets forth 30 amino acids of the 42 amino acid signal sequence and the sequence of the mature LHR-A of CR1. The mature LHR-A of CR1 starts at position 43 at the glutamine residue (Q). See the last sentence of the penultimate paragraph on page 5 of the specification.

(b) and (c) The examiner questioned which amino acids would be substituted. Applicants have amended the claims to recite that the numbering convention is based upon the mature LHR-A. See pages 4-5 of the specification.

(d) The examiner believes that the term "derivatives" is indefinite. The examiner further states that he cannot suggest another term. However, the examiner does correctly address the remaining recitations in the claim, which define the derivatives as comprising SCR polypeptides and membrane binding elements. Thus, the skilled person would know the identity and make-up of the constituents of the derivatives, and therefore would immediately understand what the recited derivative is.

(e) The examiner considered the phrase "thermodynamic additivity" to be indefinite, and stated that the Murphy article does not employ this term. In the previous response, Applicants also cited to Dill, *J. Biol. Chem.* 272: 701-04 (1997), which discusses thermodynamic additivity at the left column of page 701.

Accordingly, the subject phrase is known the art and its meaning is readily ascertainable. .

Applicants submit that the claims are definite, and therefore all rejections made pursuant to the second paragraph of Section 112 should be withdrawn.

Claim 43 is enabled

On pages 4-5 of the office action, the examiner rejected claim 43 as non enabled due to the mention of screening random chemical libraries. Applicants traverse this rejection.

Section 112 mandates that patent applications contain the "manner and process of making and using" the invention. The courts have considered applications in compliance with section 112 where the person of skill in the art can practice the invention without undue experimentation. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986). The test is not whether experimentation is necessary, but whether any experimentation would be undue in view of what type and amount of experimentation is usual in that particular field. *See* MPEP §§ 2164.05 (a-b), 2164.06 (August 2001). Routine design choices cannot be equated with non-enablement.

Thus, the burden to establish an enablement rejection rests with the Examiner. *See* MPEP §§ 2164.01; 2164.04 (August 2001). As explained by the Federal Circuit in considering the intertwined issues of enablement and utility:

> [I]t follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure.

> Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the inventor's asserted utility. * * * Taking these facts — the nature of the invention and the PTO's proffered evidence — into consideration we conclude that one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face. The PTO has not satisfied its initial burden. ***Accordingly, applicants should not be required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of § 112.***

In re Brana, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (emphasis added), *citing In re Marzocchi*, 169 USPQ 367, 369-70 (CCPA 1971).

Applicants submit that the Examiner has not met this burden, as explained below.

The specification discloses phage display and biopanning as approaches for generating random chemical libraries. See the second full paragraph on page 11. The synthesis will rely upon the nature of the target cell membrane, and the screening can be performed via straightforward binding assays. The skilled person at the time was well-equipped to undertake these procedures. In fact, applicants even provide citations to relevant journal papers on these subjects. Accordingly, applicants do not see how the skilled person would need incur undue experimentation in performing procedures commonly undertaken in the field. Rather, the efforts involved would be considered routine -- thus not undue -- and therefore the rejection should be withdrawn.

Applicants further submit that the decision in *Ex parte Mark*, 12 USPQ2d 1904 (Bd. Pat. App. Int. 1989) is instructive here. The *Mark* appellants

presented claims to a mutein of a "biologically active protein" where at least one cysteine residue that was "non-essential to said biological activity" was "substituted by another amino acid." In reversing the examiner on enablement grounds, the Board reasoned that:

> To the extent that the examiner is concerned that undue experimentation would be required to determine other proteins suitable for use in the present invention, we find [the] declaration to be persuasive that only routine experimentation would be needed for one skilled in the art to practice the invention for a given protein. The fact that a given protein might not be amenable for use in the present invention in that the cysteine residues are needed for biological activity does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a given protein are needed for retention of biological activity.

Ex parte Mark, 12 USPQ2d at 1907.

The claims in *Mark* were quite broad because they pertained to **any** protein with **any** type of biological activity, whereas applicants' claims are directed to a derivative that comprises membrane binding elements obtainable by the disclosed techniques. In view of the foregoing, applicants respectfully request withdrawal of the rejection.

The claims are not suggested by the prior art

On page 5-6 of the Office Action, the examiner rejected claims 28, 29, and 50 as obvious over U.S. Patent No. 5,545,619 in combination with Hourcade *et al.*, *J. Biol. Chem.* 265(2):974-980 (1990). The examiner alleges that the '619 patent discloses soluble polypeptides that comprise 1-4 SCRs, and that

Hourcade discloses mutations in the SCR sequences. On page 7, the examiner rejected claims 43 and 49 over the '619 patent, Hourcade and Clissold *et al.*, *Eur. J. Immunol.*, 23: 2346-52 (1993). Applicants respectfully traverse these rejections.

Applicants reiterate that the examiner must show all of the recited claim elements in the combination of references that make up the rejection. When combining references to make out a *prima facie* case of obviousness, the Examiner is obliged to show by citation to specific evidence in the cited references that (i) there was a suggestion/motivation to make the combination and (ii) there was a reasonable expectation that the combination would succeed. Both the suggestion/motivation and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *W.L Gore v. Garlock, Inc.*, 220 USPQ 303, 312-13 (Fed. Cir. 1983) (holding that is improper in combining references to hold against the inventor what is taught in the inventor's application); *see also* MPEP §§ 2142-43 (August 2001). Thus, the Examiner must provide evidentiary support based upon the contents of the prior art to support all facets of the rejection, rather than just setting forth conclusory statements, subjective beliefs or unknown authority. *See In re Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002).

When an examiner alleges a *prima facie* case of obviousness, such an allegation can be overcome by showing that (i) there are elements not contained

in the references or within the general skill in the art, (ii) the combination is improper (for example, there is a teaching away or no reasonable expectation of success) and/or (iii) objective indicia of patentability exist (for example, unexpected results). *See U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*, 230 USPQ 416, 419-20 (Fed. Cir. 1986). Applicants submit that the rejection does not satisfy these requirements.

The '619 Patent

The '619 patent discloses "RCA protein analogs," which comprise CR1-4 analogs (note that this is distinct from SCR). See Example 2. The focus of the '619 patent is on SCR-1, SCR-2, SCR-8 and SCR-9. See column 10, lines 45-47. A review of the '619 patent shows that there is no disclosure of soluble proteins that comprise SCR3.

Applicants' claims also recite a specific set of possible amino acid substitutions, namely:

> Val at position 4, Asp at position 19, Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, His at position 236.

These substitutions are not taught or suggested by the brief passage contained in column 7, lines 6-9 of the '619 patent.

Hourcade

Hourcade presents an analysis of the amino-terminal coding region of CR1, and reports on a "CR-1 like protein." This protein is discussed on pages 4-5 of applicants' specification. Hourcade only notes that the CR-1 like protein might be an uncharacterized complement protein or an unexpressed pseudogene. See page 979. Hourcade points to no usefulness of the CR-1 like protein, at least on the context of CR-1.

Clissold

Clissold concerns the expression of CR1 anchored at a cell surface by a glycolipid anchor. See the Clissold abstract. By definition, Clissold does not describe a soluble polypeptide. Moreover, Clissold does not disclose the amino acid substitutions recited in the claims.

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Turning now to the first rejection, the '619 patent does not disclose the presence of SCR-3 or the specific types of substitutions in a soluble polypeptide. These deficiencies are not rectified by Hourcade, which discloses a CR-1 like protein, but does not disclose a soluble polypeptide, much less any functionality for the CR-1 like protein. Finally, the examiner provides no demonstration of a suggestion or motivation to base substitutions in CR-1 based upon the CR-1 like protein, particularly given the fact that Hourcade believes the gene encoding the CR-1 like protein may be a pseudogene and not expressed at all. In fact, the top of right column on page 979 of Hourcade states that CR-1 like transcripts have not been found. Thus, the skilled person is provided with no motivation or

suggestion to modify native sequences with sequences found in a possibly existing protein of undetermined functionality. Such a combination can hardly be said to provide the skilled person with a reasonable expectation of successfully practicing the claimed invention.

The second rejection suffers from all of the deficiencies of the first rejection. Additionally, Clissold provides an anchored protein, which is the antithesis of a soluble protein, and thus Clissold teaches away from the invention as claimed. *See In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994) (stating, "[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant"). Thus, Clissold provides evidence of non-obviousness, rather than obviousness.

Request

Applicants submit that the claims are in condition for allowance, and respectfully request favorable consideration to that effect. The examiner is invited to contact the undersigned at (202) 912-2000 should there be any questions.

Respectfully submitted,

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MARKED UP COPY OF AMENDED CLAIMS

28. (Twice amended) A soluble polypeptide comprising in sequence three short consensus repeats (SCR) of long homologous repeat A (LHR-A) **(SEQ ID NO: 59)** selected from the group consisting of SCR 1, 2, 3, and 4, and including at least SCR3, wherein at least one of the **SCR** native amino acids **[of the SCR (SEQ ID NO: 59)]** is substituted, wherein the **[substitution] substitute amino acid** is selected from the group consisting of Val at position 4, Asp at position 19, Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, and His at position 236**, wherein each position is based upon the mature LHR-A sequence**.

29. (Twice amended) The polypeptide according to claim 28 **[that comprises SCR] , wherein the polypeptide comprises one** selected from the group consisting of SCR 1, 2, 3 and 4 of LHR-A or SCR 1, 2 and 3 of LHR-A.

42. (Twice amended) A soluble derivative of a soluble polypeptide **[(SEQ ID NO: 59)]**, wherein said soluble derivative comprises in sequence three short consensus repeats (SCR) of long homologous repeat A (LHR-A) **(SEQ ID NO: 59)** selected from the group consisting of SCR 1, 2, 3, and 4, and including at least SCR3, wherein at least one of the **SCR** native amino acids **[of the SCR (SEQ ID NO: 59)]** is substituted, wherein the **[substitution] substitute amino acid** is selected from the group consisting of Val at position 4, Asp at position 19, Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, His at position 236, **wherein each position is based upon the mature LHR-A sequence, and**

wherein said soluble **[polypeptide] derivative** comprises at least two heterologous membrane binding elements with low membrane affinity covalently associated with the polypeptide, wherein the elements are capable of interacting independently and with thermodynamic additivity with components of cellular membranes exposed to extracellular fluids, **and**

wherein the membrane binding elements have an affinity with a dissociation constant of between at least about 1μM and 1mM.

49. (Twice amended) A process for preparing a soluble derivative of a soluble polypeptide **[(SEQ ID NO: 59)]**, wherein said soluble derivative comprises in sequence three short consensus repeats (SCR) of long homologous repeat A (LHR-A) **(SEQ ID NO: 59)** selected from the group consisting of SCR 1, 2, 3, and 4, and including at least SCR3, wherein at least one of the **SCR** native amino acids **[of the SCR (SEQ ID NO: 59)]** is substituted, wherein the **[substitution] substitute amino acid** is selected from the group consisting of Val at position 4, Asp at position 19, Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, His at position 236, **wherein each position is based upon the mature LHR-A sequence,** comprising

expressing DNA encoding the polypeptide portion of said derivative in a recombinant host cell and recovering the product and thereafter post translationally modifying the polypeptide to **[chemically introduce] bind** membrane binding elements **to the polypeptide**.

50. (Twice amended) A pharmaceutical composition comprising (A) a therapeutically effective amount of a soluble polypeptide comprising in sequence three short consensus repeats (SCR) of long homologous repeat A (LHR-A) **(SEQ ID NO: 59)** selected from the group consisting of SCR 1, 2, 3, and 4, and including at least SCR3, wherein at least one of the **SCR** native amino acids **[of the SCR (SEQ ID NO: 59)]** is substituted, wherein the **[substitution] substitute amino acid** is selected from the group consisting of Val at position 4, Asp at position 19, Ser at position 53, Lys at position 57, Ala at position 74, Asp at position 79, Arg at position 84, Pro at position 91, Asn at position 109, Lys at position 116, Val at position 119, Ala at position 132, Thr at position 137, Ile at position 139, Ser at position 140, Tyr at position 143, His at position 153, Leu at position 156, Arg at position 159, Lys at position 161, Lys at position 177, Gly at position 230, Ser at position 235, His at position 236, **wherein each position is based upon the mature LHR-A sequence,** and (B) a pharmaceutically acceptable carrier or excipient.